

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 October 2003 (30.10.2003)

PCT

(10) International Publication Number
WO 03/088962 A1

- (51) International Patent Classification⁷: **A61K 31/426**, 31/216, 31/22, 31/397, A61P 3/10, 3/06
- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (21) International Application Number: **PCT/US03/11896**
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: **15 April 2003 (15.04.2003)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
60/373,091 16 April 2002 (16.04.2002) US
60/387,031 7 June 2002 (07.06.2002) US
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **MOLLER, David, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **WRIGHT, Samuel, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/088962 A1

(54) Title: **COMBINATION THERAPY USING A PPAR ALPHA/GAMMA AGONIST**

(57) Abstract: The present invention relates to pharmaceutical compositions comprising a combination of a first drug which is a PPAR α/γ dual agonist and a second drug which is selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, (7) an ACAT inhibitor, and (8) a CTEP inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients, and a pharmaceutically acceptable carrier. Such combinations are useful for treating hyperglycemia, lipid disorders, and obesity in patients who have type 2 diabetes, metabolic syndrome, insulin resistance, and impaired glucose tolerance.

TITLE OF THE INVENTION**COMBINATION THERAPY USING A PPAR ALPHA/GAMMA AGONIST****FIELD OF THE INVENTION**

5 The instant invention is concerned with the use of combinations of pharmaceutically active compounds that are agonists of the alpha and gamma subtypes of the peroxisome proliferator activated receptor (PPAR) with other compounds that are active in reducing cholesterol and/or other lipids, such as cholesterol absorption inhibitors and statins.

10

BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors that is characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state or after administration of glucose during an oral glucose tolerance
15 test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with type 2 diabetes mellitus often have elevated levels of lipids, such as cholesterol and
20 triglycerides, and have poor lipid profiles, with high levels of LDL-cholesterol and low levels of HDL-cholesterol, and are at an especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid metabolism
25 and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

Patients having type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), often have plasma insulin levels that are the same or even elevated compared with nondiabetic patients; however, these patients have developed a
30 resistance to the effectiveness of insulin in stimulating glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues. The plasma insulin levels, while normal or elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is caused by a post-insulin receptor binding defect
35 that is not well understood. Insulin resistance results in insufficient insulin activation

of glucose uptake, oxidation and storage in muscle, and also causes inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for type 2 diabetes have well-known
5 limitations. Physical exercise and a reduction in dietary intake of calories can dramatically improve the diabetic condition, but compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption. The plasma level of insulin can be increased by administration of
10 sulfonylureas (e.g. tolbutamide and glipizide), which stimulate the pancreatic β -cells to secrete more insulin, and/or by injection of insulin as the response to sulfonylureas diminishes in effectiveness and eventually fails. However, dangerously low levels of plasma glucose can result from these last two treatments, and insulin resistance can continue to increase due to the even higher plasma insulin levels. The biguanides can improve the response to insulin, resulting in some correction of hyperglycemia.
15 However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea, respectively.

The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently developed class of compounds which have a novel mode of action in ameliorating many symptoms of type 2 diabetes. These agents substantially increase
20 insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes, resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. Some glitazones not only improve insulin sensitivity, but also alleviate disorders of lipid metabolism.

Metabolic abnormalities may also affect glucose homeostasis even in
25 patients who are not diabetic. A patient may have impaired glucose tolerance if the patient's fasting plasma glucose is less than the level that is used to establish type 2 diabetes but is nevertheless higher than the accepted normal range. Such patients are at risk of developing type 2 diabetes, often are insulin resistant, and often have lipid disorders and other cardiovascular risk factors.

30 Many diabetic and non-diabetic insulin resistant patients also have a combination of lipid and non-lipid cardiovascular risk factors that are characteristic of the metabolic syndrome, which was recently assigned criteria for clinical identification in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood
35 Cholesterol in Adults (Adult Treatment Panel III, or ATP III), JAMA, May 16, 2001,

Vol. 285, No. 19, pp 2486-2497; see particularly Table 8 at p. 2493. Briefly a patient has the metabolic syndrome when the patient has 3 of the following 5 defining criteria: 1) abdominal obesity; 2) elevated triglycerides; 3) low HDL cholesterol; 4) high blood pressure; and 5) elevated fasting glucose. These criteria are clinically defined in the report. Metabolic syndrome is believed to be closely linked to insulin resistance

Disorders of lipid metabolism or dyslipidemias include various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as Low Density Lipoproteins (LDL), Very Low Density Lipoproteins (VLDL) and Intermediate Density Lipoproteins (IDL). Cholesterol is mostly carried in Low Density Lipoproteins (LDL), and this component is commonly known as the "bad" cholesterol because it has been shown that elevations in LDL-cholesterol correlate closely to the risk of coronary heart disease. A smaller component of cholesterol is carried in the High Density Lipoproteins (HDL) and is commonly known as the "good" cholesterol. In fact, it is known that the primary function of HDL is to accept cholesterol deposited in the arterial wall and to transport it back to the liver for disposal through the intestine. It is therefore desirable to lower elevated levels of LDL cholesterol and to concurrently increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with a lower risk of coronary heart disease (CHD). See, for example, Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373-381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, a drug with limited utility because doses that increase HDL are associated with undesirable effects, such as flushing.

Dyslipidemias were originally classified by Fredrickson according to which lipids were altered, as mentioned above. The Fredrickson classification includes 6 phenotypes (i.e., I, IIa, IIb, III, IV and V) with the most common being the isolated hypercholesterolemia (or type IIa) which is usually accompanied by elevated concentrations of total and LDL cholesterol. The initial treatment for hypercholesterolemia is often to modify the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone

A second common form of dyslipidemia is the mixed or combined hyperlipidemia or type IIb and III of the Fredrickson classification. This dyslipidemia is often prevalent in patients with type 2 diabetes, obesity and the metabolic syndrome. In this dyslipidemia there are modest elevations of LDL-cholesterol, accompanied by more pronounced elevations of small dense LDL-cholesterol particles, VLDL and/or IDL (i.e., triglyceride rich lipoproteins), and total triglycerides. In addition, concentrations of HDL are often low.

Peroxisome proliferators are a structurally diverse group of compounds that when administered to rodents elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes of the beta-oxidation cycle. Compounds that are agonists of the peroxisome proliferator activated receptor include but are not limited to the fibrate class of lipid modulating drugs, certain herbicides and phthalate plasticizers. The glitazones (5-benzylthiazolidine-2,4-diones) are generally believed to exert their effects through binding to peroxisome proliferator activated receptors (PPAR's). Peroxisome proliferation is also triggered by dietary and physiological factors such as a high-fat diet and cold acclimatization. It is generally believed that the glitazones exert their effects by binding to the peroxisome proliferator activated receptor (PPAR) family of receptors, controlling certain transcription elements having to do with the biological entities discussed above. See Hulin et al., Current Pharm. Design (1996) 2, 85-102.

Three sub-types of peroxisome proliferator activated receptor (PPAR) have been discovered and described: peroxisome proliferator activated receptor alpha (PPAR α), peroxisome proliferator activated receptor gamma (PPAR γ), and peroxisome proliferator activated receptor delta (PPAR δ). PPAR α is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β -oxidation of fatty acids. PPAR α is also associated with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives, such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, each of which is a PPAR α ligand and/or activator, produces a substantial reduction in plasma triglycerides as well as some increase in HDL. The effects on LDL cholesterol are inconsistent and might depend upon the compound and/or the dyslipidemic phenotype. For these reasons, this class of compounds has been primarily used to treat hypertriglyceridemia (i.e, Fredrickson Type IV and V) and/or mixed hyperlipidemia.

The PPAR γ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. Prostaglandin J₂ derivatives and various long chain fatty acids have been identified as potential natural ligands of the PPAR γ subtype. The glitazone thiazolidinedione-based antidiabetic agents have a high affinity for the PPAR γ receptor.

The human nuclear receptor gene PPAR δ (hPPAR δ) has been cloned from a human osteosarcoma cell cDNA library and is fully described by A. Schmidt et al., *Molecular Endocrinology*, 6 :1634-1641 (1992). In general, the exact role of PPAR δ is less well understood than the other PPAR sub-types, and fewer PPAR δ agonists have been developed and studied. There have been recent reports of PPAR δ agonists that are active in treating type 2 diabetes, dyslipidemia, and inflammation, such as occurs in rheumatoid arthritis.

Two glitazones (rosiglitazone and pioglitazone) are currently approved for use in the treatment of diabetes. These two glitazones are primarily or exclusively PPAR γ agonists. A third glitazone, troglitazone, was withdrawn by the manufacturer due to problems with liver toxicity. Some newer glitazones that are currently under development or are in clinical trials have dual PPAR α and γ activity. These are expected to improve both insulin sensitivity and the lipid profile in patients having type 2 diabetes.

A promising class of glitazones is described in US Patent Nos. 6,030,990, 6,001,862 and 6,147,101, assigned to Kyorin Pharmaceutical, Ltd., which are incorporated by reference into this application in their entirety. The compounds described in the Kyorin patents are PPAR alpha/gamma dual agonists. They are referred to as "dual" agonists because they are agonists of both the PPAR alpha and PPAR gamma sub-types. They are effective in treating elevated serum glucose and elevated triglycerides and lipids in patients having type 2 diabetes.

Cholesterol absorption inhibitors are a relatively new class of therapeutic agents that interfere with the absorption of cholesterol from the digestive tract, and specifically from the small intestine. This decreases the amount of cholesterol passing into the bloodstream from the intestines and has the effect of reducing serum cholesterol. Their mechanism of action is different from the mechanism of action of statins, which are widely used in medications for reducing the levels of cholesterol and lipids. The statins, including simvastatin, lovastatin,

pravastatin, fluvastatin, atorvastatin, and rosuvastatin, inhibit biosynthesis of cholesterol by inhibition of the HMG CoA reductase enzyme. Their mechanism of action is also different from that of PPAR α/γ dual agonists, which reduce triglycerides and lipids through agonism of the PPAR α receptor.

- 5 A generic class of active cholesterol absorption inhibitors is described in US Patents 5,767,115, 5,631,365, and 5,846,966, all of which are assigned to Schering Corporation and are incorporated into this application by reference in their entirety.

10 SUMMARY OF THE INVENTION

- The present invention relates to the treatment of type 2 diabetes (non-insulin dependent diabetes mellitus, or NIDDM) and to various disorders associated with type 2 diabetes, by the administration of the combination of active ingredients described below. The invention further relates to the treatment (reduction) of
- 15 hyperglycemia that is associated with type 2 diabetes by administration of the combination of active ingredients described below. The invention further relates to the treatment of insulin resistance and/or impaired glucose tolerance that are associated with type 2 diabetes or that are associated with a pre-diabetic condition or that are a symptom of the metabolic syndrome, which is also known as syndrome X,
- 20 by administration of the combination of active ingredients described below. The invention further relates to the treatment of one or more other diseases or conditions that often accompany type 2 diabetes, including lipid disorders, such as mixed or diabetic dyslipidemia, isolated hypercholesterolemia, elevated LDL-C and/or non-HDL-C, elevated hyperapoB lipoproteinemia, hypertriglyceridemia, elevated triglyceride-
- 25 rich-lipoproteins, and low HDL cholesterol, by administration of the combination of active ingredients described below. The invention further relates to the treatment or amelioration of atherosclerosis and obesity by administration of the combination of active ingredients described below. Administration of the combination of active ingredients described below may also delay the onset or reduce the risk of
- 30 atherosclerosis and obesity. The diseases listed above are treated or controlled or ameliorated by administration of a combination of a therapeutically effective amount of a PPAR α/γ dual agonist and a therapeutically effective amount of a second active drug, which is selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4)
- 35 nicotinic alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic

anti-oxidant, (7) an ACAT inhibitor, and (8) a CETP inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

These combinations are useful in reducing hyperglycemia in the treatment of type 2 diabetes mellitus, which is often referred to as non-insulin dependent diabetes (NIDDM), and in reducing levels of lipids or improving the lipid profile in the treatment of dyslipidemia and other lipid disorders that are often associated with type 2 diabetes or that often occur in a diabetic or a pre-diabetic patient who is insulin resistant, such as hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, high LDL cholesterol, insulin resistance, impaired glucose tolerance, and obesity.

The invention also relates to the use of the combinations described herein for the manufacture of a medicament for reducing hyperglycemia in type 2 diabetes mellitus and for reducing levels of lipids or improving the lipid profile in dyslipidemia and other lipid disorders that are often associated with type 2 diabetes or that often occur in a diabetic or a pre-diabetic patient who is insulin resistant, such as hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, high LDL cholesterol, insulin resistance, impaired glucose tolerance, and obesity.

20 DETAILED DESCRIPTION OF THE INVENTION

PPAR agonists are classified as PPAR α agonists, PPAR γ agonists, or PPAR α/γ dual agonists, based on the relative potencies of the compounds as agonists of the PPAR α and PPAR γ receptors. PPAR γ agonists are those compounds that exhibit $\geq 50\%$ of the maximal effects of rosiglitazone, a potent PPAR γ agonist, on human PPAR γ . PPAR α agonists are those compounds that exhibit $\geq 50\%$ of the maximal effects of fenofibrate, a potent PPAR α agonist, on human PPAR α . Concentration potencies are measured by using the cell-based transactivation assay or cell-free co-activator association assay, which are described herein below.

PPAR α/γ dual agonists are compounds that exhibit both significant PPAR α and PPAR γ agonism, as defined above, wherein the half-maximal concentration potencies (EC₅₀) for activation of hPPAR γ and the half-maximal concentration potencies (EC₅₀) for activation of hPPAR α differ by less than 30-fold.

Compounds that exhibit significant PPAR α and/or PPAR γ agonism, as defined above, wherein the half-maximal concentration potencies (EC₅₀) for activation of hPPAR γ and the half-maximal concentration potencies (EC₅₀) for

activation of hPPAR α differ by more than 30-fold are defined as selective PPAR α or selective PPAR γ agonists.

For example, a compound that exhibits $\geq 50\%$ of the maximal effects of rosiglitazone on human PPAR γ and therefore exhibits significant PPAR γ agonism, and which exhibits a half-maximal concentration potency (EC₅₀) for activation of hPPAR γ which is greater than 30-fold higher than its half-maximal concentration potency (EC₅₀) for activation of hPPAR α is defined as a selective PPAR γ agonist. Rosiglitazone is an example of such a compound. Likewise, a compound that exhibits $\geq 50\%$ of the maximal effects of fenofibrate on human PPAR α and therefore exhibits significant PPAR α agonism, and which exhibits a half-maximal concentration potency (EC₅₀) for activation of hPPAR α which is greater than 30-fold higher than its half-maximal concentration potency (EC₅₀) for activation of hPPAR γ is defined as a selective hPPAR α agonist. Fenofibrate is an example of such a compound.

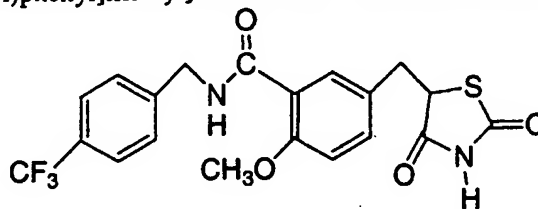
Preferred PPAR α/γ dual agonists are compounds that exhibit both significant PPAR α and PPAR γ agonism, as defined above, wherein the half-maximal concentration potencies (EC₅₀) for activation of hPPAR γ and the half-maximal concentration potencies (EC₅₀) for activation of hPPAR α differ by less than 20-fold.

A more preferred group of PPAR α/γ dual agonists are compounds that exhibit both significant PPAR α and PPAR γ agonism, as defined above, wherein the half-maximal concentration potencies (EC₅₀) for activation of hPPAR γ and the half-maximal concentration potencies (EC₅₀) for activation of hPPAR α differ by less than 10-fold. These are the "balanced PPAR α/γ dual agonists."

PPAR γ agonists generally improve insulin sensitivity, thereby reducing the hyperglycemia that is symptomatic of type 2 diabetes. PPAR α agonists improve lipid metabolism by lowering triglycerides, lowering LDL, and potentially raising HDL. PPAR α/γ dual agonists can control or ameliorate both the hyperglycemia and dyslipidemia that are associated with type 2 diabetes. The preferred PPAR α/γ dual agonists for combination therapy with cholesterol absorption inhibitors and other hypolipemic compounds are "balanced" PPAR α/γ dual agonists, as defined above. These have approximately equal potencies (within a factor of 10) for agonism of both the PPAR α and PPAR γ receptor sub-types.

Preferred PPAR α/γ dual agonists are disclosed and claimed in the Kyorin patents cited above, such as US 6,030,990. The most preferred balanced PPAR α/γ dual agonist for this invention is disclosed in Example 39 of US 6,030,990. This compound is known generally in the pharmaceutical industry as KRP-297. The

chemical name of KRP-297 is 5-[(2,4-dioxo-5-thiazolidinyl)methyl]-2-methoxy-*N*-[[4-(trifluoromethyl)phenyl]methyl]-benzamide. The structure is shown below:



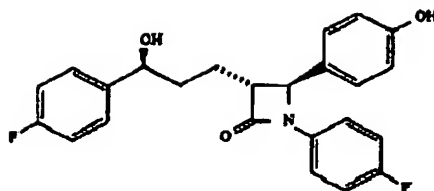
KRP-297

5 The PPAR α / γ dual agonists of this invention are used in combination with one or more other drugs that may be used to treat lipid disorders, such as hypertriglyceridemia, hyperlipidemia, hypercholesterolemia, and dyslipidemia. The other drug(s) in these combinations is(are) selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid
10 sequestrant, (4) nicotinic alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, (7) an ACAT inhibitor, and (8) a CETP inhibitor, including pharmaceutically acceptable salts of one or more active ingredients. The other drug(s) is(are) described in more detail below:

(1) Cholesterol absorption inhibitors, also known as sterol absorption
15 inhibitors, interfere with the absorption of cholesterol from the digestive tract, and specifically from the small intestine. This decreases the amount of cholesterol passing into the bloodstream from the intestines and has the effect of reducing serum cholesterol. The combination of cholesterol absorption inhibitors and PPAR α / γ dual agonists has the effect of reducing serum cholesterol by two independent mechanisms
20 (PPAR α agonism and inhibition of cholesterol absorption). At the same time, the PPAR α / γ dual agonist also reduces hyperglycemia associated with type 2 diabetes.

Examples of cholesterol absorption inhibitors include stanol esters, beta-sitosterol, sterol glycosides such as tiqueside, and azetidinones, such as the class of compounds described below. A preferred class of cholesterol absorption inhibitors
25 is described in the Schering patents cited above, including US 5,767,115.

The most preferred cholesterol absorption inhibitor for practicing this invention is disclosed as Example 6A in US 5,767,115. The compound is known generally in the pharmaceutical industry as ezetimibe, the chemical name of which is 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-
30 hydroxyphenyl)-2-azetidinone. The structure follows:



Ezetimibe

(2) HMG-CoA reductase inhibitors are well known in the pharmaceutical field as being effective at reducing the rate of biosynthesis of cholesterol by the liver. HMG-CoA reductase inhibitors include the statins, which have been successfully used in the treatment of lipid disorders. Statins that can be used in the combination therapies of this invention include, but are not limited to, lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, cerivastatin, and ZD-4522.

(3) Bile acid sequestrants, such as cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran polymer, also including Colestid®, LoCholest®, and Questran®, are polymeric anion exchange resins that interfere with reabsorption of bile acid into the liver. The liver compensates for the decreased availability of bile acid by converting cholesterol into bile acid salts, thereby reducing the amount of cholesterol.

(4) Nicotinyl alcohol, nicotinic acid, niacin, and salts thereof, can increase HDL and reduce LDL at relatively high doses, so that the overall lipid profile is better. Flushing is a common side effect that limits the usefulness of these compounds in therapy.

(5) PPAR α agonists, such as fibric acid derivatives (clofibrate, fenofibrate and bezafibrate) and gemfibrozil, reduce lipids and cholesterol by agonism of the PPAR α receptor. This is the same mechanism as the PPAR α agonism that occurs with the PPAR α / γ dual agonists. Other PPAR α agonists include beclofibrate, ciprofibrate, etofibrate, gemcabene, GW7647, BM 170744, LY518674, Atromid®, Lopid®, and Tricor®.

(6) Acyl CoA:cholesterol acyltransferase inhibitors (ACAT inhibitors), such as for example avasimibe, eflucimide, KY505, and SMP 797, inhibit the ACAT enzyme, which catalyzes the formation of cholesteryl esters (CE's) from cholesterol and long chain fatty acids. CE's accumulate in smooth muscle cells and macrophages

and can be incorporated into arterial wall lesions, which contribute to atherosclerosis. Inhibition of the enzyme inhibits this process by decreasing the availability of CE's.

(7) Phenolic anti-oxidants, such as probucol, reduce plasma cholesterol, LDL- cholesterol, and HDL- cholesterol. They also inhibit oxidative
5 modification of LDL-cholesterol. Oxidative modification of LDL-cholesterol is an important step in the progression of atherosclerosis.

(8) Cholesterol Ester Transfer Protein (CETP) facilitates the movement of cholesteryl esters and triglycerides between lipoproteins in the blood, including high density lipoproteins (HDL), low density lipoproteins (LDL), and very
10 low density lipoproteins (VLDL). CETP facilitates the transfer of cholesteryl esters from HDL to LDL, resulting in a net increase of LDL and VLDL and a net decrease of HDL. Increases in LDL and VLDL and decreases in HDL are generally believed to favor atherogenesis. CETP inhibitors are compounds that inhibit CETP, so that there is an increase in HDL and a decrease in LDL and VLDL. There are currently no
15 CETP inhibitors that are being marketed. Examples of developmental CETP inhibitors include JTT-705, torcetrapib, CP532,632, BAY63-2149, SC-591, SC-795, SC-744, SC-144, wiedenols, Sch-50678, strongylin A, Sch-50679, Sch-50680, s-triazines, teracyclic catechols, and Sch-58149. There is also a developmental vaccine CETi-1 that is being developed by AVANT Immunotherapeutics. CETi-1 is
20 apparently in phase II trials.

Other lipid lowering agents that may be used in the combinations of this invention as the second active component rather than or in addition to those listed above include:

- (1) HMG-CoA synthase inhibitors;
- 25 (2) Squalene synthetase inhibitors;
- (3) FXR receptor antagonists such as GW 4064, and SR 103912;
- (4) LXR receptor agonists such as GW 3965, T9013137, and XTCO179628;
- (5) Renin angiotensin system inhibitors;
- (6) Microsomal triglyceride transport inhibitors;
- 30 (7) Bile acid reabsorption inhibitors, such as BARI 1453, SC435, PHA384640, S8921, and AZD7706;
- (8) PPAR δ agonists such as GW 501516, and GW 590735;
- (9) Triglyceride synthesis inhibitors;
- (10) MTTP inhibitors, such as inplitapide, LAB687, and CP346086;
- 35 (11) Transcription modulators;

- (12) Squalene epoxidase inhibitors;
- (13) Low density lipoprotein (LDL) receptor inducers; and
- (14) Platelet aggregation inhibitors.

The use of the above combinations is expected to be beneficial in a patient with severe hypertriglyceridemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, and/or other lipid disorders. The lipid lowering drugs that are listed above can be used in combination with the PPAR α / γ dual agonists to induce beneficial lipid effects. The lipid lowering drugs listed above have mechanisms that are different than the mechanism that is in effect with the PPAR α / γ dual agonists. As a result of the different mechanisms of action, the lipid lowering effects are likely to be additive for these combinations. Therefore, the doses of the PPAR α / γ dual agonist and the other lipid lowering agent may not need to be increased to levels that are higher than are normally used in order to achieve a greater lipid reduction or to achieve a greater adjustment in the lipid profile. The quantity of each individual component of the combination may even be less than is normally used. This minimizes the possibility of obtaining undesirable side effects. Note that the use of fibrates and other PPAR α agonists in combination with PPAR α / γ dual agonists is in part an exception to this generalization about mechanisms of action in that the fibrates and other PPAR α agonists have PPAR α agonism in common with the PPAR α / γ agonists. Fibrates and other PPAR α agonists do not have PPAR γ agonism in common with PPAR α / γ dual agonists, and there may still be benefits in using the two classes of compounds together.

In some cases, the combinations may also exhibit "synergy," which is defined as results that are better than additive. When there is synergy, the synergistic results may be apparent in studies using limited numbers of patients. Studies with large numbers of patients may be needed to show that the improvements are significantly better (statistically) than additive.

A highly preferred embodiment of this invention is the combination of KRP-297 with one or more of the classes of drugs that are effective in reducing or controlling hypertriglyceridemia, hypercholesterolemia, hyperlipidemia, and dyslipidemia, as listed above. In particular, the most preferred embodiments are directed to combinations of KRP-297 with one or more compounds selected from the group consisting of ezetimibe, lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522, cholestyramine, colestipol, nicotiny alcohol, nicotinic acid, clofibrate, fenofibrate, bezafibrate, gemfibrozil,

avasamibe, and probucol, or pharmaceutically acceptable salts of one or more of these compounds. In the combination therapies described above, the most preferred PPAR α / γ dual agonist is KRP-297. Pharmaceutical compositions comprising the combinations of active compounds described above and a pharmaceutically acceptable carrier have utility as therapeutic compositions, and are preferred compositions.

Preferred embodiments also relate to the administration of a combination of a therapeutically effective amount of KRP-297 and one or more compounds selected from the group consisting of ezetimibe, lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522, cholestyramine, colestipol, nicotinic alcohol, nicotinic acid, clofibrate, fenofibrate, bezafibrate, gemfibrozil, avasamibe, and probucol, or pharmaceutically acceptable salts of one or more of these compounds, for the reduction of hyperglycemia resulting from type 2 diabetes, or for the reduction of dyslipidemia, hyperlipidemia, hypertriglyceridemia, and/or hypercholesterolemia that is associated with type 2 diabetes, or both.

A pharmaceutical composition of this invention may "consist essentially of" a single PPAR α / γ dual agonist, such as KRP-297, in combination with a second single active compound selected from the compounds listed above, such as ezetimibe or a statin. Furthermore, the compositions may also include a pharmaceutically acceptable carrier. "Consist essentially of" means that other ingredients besides those named can be present, provided that the other ingredients do not change the basic and novel characteristics of the composition.

A preferred pharmaceutical composition consists essentially of KRP-297, ezetimibe, and a pharmaceutically acceptable carrier. Another preferred pharmaceutical composition consists essentially of KRP-297, simvastatin, and a pharmaceutically acceptable carrier. A third preferred pharmaceutical composition consists essentially of KRP-297, simvastatin, ezetimibe, and a pharmaceutically acceptable carrier.

The combinations disclosed herein may be used as the primary treatment for type 2 diabetes and associated disorders, or the combination may be used as an adjunct to diet and exercise to improve glycemic control in patients who have type 2 diabetes and concurrently to control or ameliorate the dyslipidemia, hyperlipidemia, hypercholesterolemia and other lipid disorders that often occur in diabetic patients.

The combinations are expected to be particularly effective in treating patients with type 2 diabetes and Fredrickson types IIa, IIb, III, IV, and V hyperlipidemia. The combinations are expected to reduce elevated total-cholesterol, LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B, and TG, and to increase
5 HDL-C and Apolipoprotein A-1 and A-11.

The combinations of pharmaceuticals of this invention can also be used in combination with other oral anti-hyperglycemic agents, including sulfonylureas, metformin and insulin, when the combination alone or with diet and exercise does not result in adequate glycemic or lipid control.

10 Briefly, the combinations as defined above are useful in treating or ameliorating hyperglycemia associated with type 2 diabetes, and for concurrently treating one or more of the following conditions that often accompany type 2 diabetes:

- (1) lipid disorders;
- (2) hyperlipidemia
- 15 (3) obesity;
- (4) hypercholesterolemia;
- (5) hypertriglyceridemia;
- (6) dyslipidemia;
- (7) low HDL cholesterol; and
- 20 (8) atherosclerosis, including sequellae of atherosclerosis, such as angina, claudication, heart attack, stroke, etc.

The combinations listed above may also be administered to patients who are not diabetic but who may have insulin resistance, impaired glucose tolerance, and/or metabolic syndrome. Since insulin resistance is one of the conditions that is
25 often present in patients with metabolic syndrome, the PPAR α / γ agonist, such as for example KRP-297, may be beneficial to the patient because the insulin sensitizing action of the PPAR α / γ agonist ameliorates the insulin resistance, thereby ameliorating some of the other symptoms of metabolic syndrome. The combinations described above may therefore ameliorate one or more of the cardiovascular risk factors in
30 patients who have metabolic syndrome, where the presence of metabolic syndrome is determined by the fact that the patient has three or more of the cardiovascular risk factors that are criteria for diagnosing metabolic syndrome. In many cases, the combinations described herein may ameliorate two or more of the cardiovascular risk factors in patients who have metabolic syndrome. In many cases, the combinations

described herein may ameliorate three or more of the cardiovascular risk factors in patients who have metabolic syndrome.

Definitions

5 "Combination" therapy or a drug "combination" means that two or more active components are administered to a patient at approximately the same time or at times that are sufficiently close that both drugs will be present concurrently in the patient at a level sufficient to be therapeutic or sub-therapeutic at certain times of the day. Combination therapy can also occur when the two medicines are
10 administered at the same time or at different times during the day. Combination therapy thus also includes therapies in which the two active drugs are administered on different overlapping schedules. A pharmaceutical composition in unit dosage form containing the two active drugs is a preferred combination when use of such a composition is practicable. Dispensing the active compounds as separate dosage
15 forms but together in the same package is another preferred means of dispensing a combination according to this invention.

The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s) and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or
20 indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing the compounds of the present invention and a pharmaceutically
25 acceptable carrier.

The term "metabolic syndrome" is defined in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), JAMA, May 16, 2001, Vol. 285, No. 19, pp 2486-2497,
30 discussed herein in the Background of the Invention section. Other medical terms and diseases (e.g. type 2 diabetes) have widely accepted definitions in the medical field.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

The active ingredients in the combinations of this invention may
35 contain one or more asymmetric centers. The individual active components can thus

occur as racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all combinations of such isomeric forms. Specifically, KRP-297 is administered as a racemate. Ezetimibe is a single optically active isomer.

5 Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers, singly or as a mixture.

 Some of the compounds described herein may exist as tautomers, such as ketones and enols. The individual tautomers as well as mixtures thereof are
10 encompassed with the compounds that are described herein.

Salts The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from
15 inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable
20 organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-
25 ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

 When the compound of the present invention is basic, salts may be
30 prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the

like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds used in the combinations described herein are meant to also include the pharmaceutically acceptable salts.

Metabolites – Prodrugs

Individual compounds claimed in the combinations described herein may occur as therapeutically active metabolites of other compounds that have been administered to a patient. Such active metabolites would still be part of the claimed combination.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosages may be ascertained readily by a person skilled in the art.

When treating or ameliorating type 2 diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of this invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 0.1 milligrams to about 1000 milligrams, preferably from about 1 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 1 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response for the patient and the specific compounds that are administered.

For a preferred embodiment, examples of daily dosages of KRP-297 and ezetimibe can be any of the following, for example: for KRP-297, 1mg, 3mg, 5 mg, 10mg, or 20 mg; and for ezetimibe, 1mg, 5mg, 10mg, 20 mg, 50 mg, or 100 mg.

5 For another preferred embodiment, examples of daily dosages of KRP-297 and simvastatin can be any of the following. For KRP-297, exemplary dosages are 1mg, 3mg, 5 mg, 10mg, or 20 mg. For simvastatin, exemplary dosages are 5mg, 10mg, 20mg, 40mg, and 80mg.

10 Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprise the compounds of this invention and a pharmaceutically acceptable carrier or carriers. The pharmaceutical compositions of the present invention comprise the compounds or pharmaceutically acceptable salts thereof, as
15 well as pharmaceutically acceptable carriers and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal,
20 topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), and pulmonary (nasal or buccal inhalation). The most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

25 The compounds of this invention can be individually combined in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, or they can be combined together in a carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous).
30 In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants,
35 binders, disintegrating agents and the like in the case of oral solid preparations such

as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of this invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier

can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

5 Combinations with a Third Therapeutic Compound

The combinations of this invention may optionally include other drugs that may also be useful in the treatment, suppression or amelioration of the diseases or conditions for which the combinations of this invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor,
10 contemporaneously or sequentially with the combination drugs of this invention. When a compound of the combination of this invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the combination of this invention is preferred. However, the combination therapy also includes therapies in which the compound of
15 this invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compound of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain
20 one or more other active ingredients, in addition to a compound of this invention.

Examples of other active ingredients that may be administered in combination with the combination of drugs of this invention, either being administered separately or in the same pharmaceutical composition, include, but are not limited to:

- 25 (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV)
30 inhibitors;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide, or related materials;
- (d) α -glucosidase inhibitors (such as acarbose);

- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fibric acid derivatives (clofibrate, fenofibrate and bezafibrate) or gemfibrozil (v) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (vi) anti-oxidants, such as probucol;
- (f) PPAR δ agonists such as those disclosed in WO97/28149;
- 10 (g) antiobesity compounds (anorectics) such as fenfluramine, dexfenfluramine, phentermine, sibutramine, mazindol, orlistat, lipase inhibitors, neuropeptide Y5 inhibitors, and β 3 adrenergic receptor agonists;
- (h) an ileal bile acid transporter inhibitor; and
- (i) agents intended for use in inflammatory conditions, such as aspirin,
- 15 non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors.

- Non-limiting examples of the combinations described above include combinations of the PPAR α/γ agonists and lipid lowering drugs of this invention with two or more other active compounds selected from biguanides, sulfonylureas,
- 20 HMG-CoA reductase inhibitors, other PPAR agonists, PTP-1B inhibitors, DP-IV inhibitors, and anti-obesity compounds.

ASSAYS

IN VIVO ASSAYS

Male db/db mice (10-11 week old C57Bl/KFJ, Jackson Labs, Bar Harbor, ME) are housed 5/cage and allowed *ad lib.* access to ground Purina rodent chow and water. The animals, and their food, are weighed every 2 days and are dosed daily by gavage with vehicle (0.5% carboxymethylcellulose) \pm test compound at the indicated dose. Drug suspensions are prepared daily. Plasma glucose, and triglyceride concentrations are determined from blood obtained by tail bleeds at 3-5 day intervals during the study period. Glucose, and triglyceride, determinations are performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:6 (v/v) with normal saline. Lean animals are age-matched heterozygous mice maintained in the same manner.

Male Golden Syrian hamsters weighing ~ 150 g are used to measure lipid modulation effects of test compounds. Hamsters are housed in boxes (5 per box), are fed a normal rodent chow diet, and are given free access to water. Compounds are suspended in 0.5% methylcellulose and gavaged daily to the hamsters for 9 days (10 hamsters per group). On the morning of the 10th day, the hamsters are euthanized with carbon dioxide, and blood samples are obtained via heart puncture. Serum levels of total cholesterol and triglycerides are determined.

Mature male beagle dogs, weighing ~15 kg on average, are used to measure the lipid modulation effects of test compounds. Dogs are housed individually, are fed a cholesterol-free chow diet, and are given free access to water. Prior to the start of experiments, samples are taken weekly from the jugular vein and the serum cholesterol levels are determined. To test the effects of compounds on serum cholesterol, compounds are suspended in 0.5% methylcellulose and gavaged daily to the dogs for 2 weeks (5 dogs per group). Blood samples are taken during and after the dosing period, and serum levels of total cholesterol and triglycerides are determined.

30

IN VITRO ASSAYSStandardized Cell-Based GAL4 Chimeric Receptor Transactivation Assay (Cell-Based Transactivation Assay)

The following assay is also described in: Berger J, Leibowitz MD, Doeber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Cullinan CA, Hayes NS, Li Y,

35

Tanen M, Ventre J, Wu MS, Berger GD, Mosley R, Marquis R, Santini C, Sahoo SP, Tolman RL, Smith RG, Moller DE. Novel peroxisome proliferator-activated receptor (PPAR γ) and PPAR δ ligands produce distinct biological effects, 1999 J Biol Chem 274: 6718-6725.

- 5 Expression constructs are prepared by inserting cDNA sequences encoding the ligand binding domains of human PPAR γ or PPAR α adjacent to the yeast GAL4 transcription factor DNA binding domain in the mammalian expression vector pcDNA3 to create pcDNA3-hPPAR γ /GAL4 and pcDNA3-hPPAR α /GAL4, respectively. The GAL4-responsive reporter construct, pUAS(5X)-tk-luc, contains 5
10 copies of the GAL4 response element placed adjacent to the thymidine kinase minimal promoter and the luciferase reporter gene. The transfection control vector, pCMV-lacZ, contains the galactosidase Z gene under the regulation of the cytomegalovirus promoter. COS-1 cells are seeded at 1.2×10^4 cells/well in 96 well plates in Dulbecco's modified Eagle medium (high glucose) containing 10% charcoal
15 stripped fetal calf serum, nonessential amino acids, 100 units/ml Penicillin G and 100 μ g/ml Streptomycin sulfate at 37°C in a humidified atmosphere of 10% CO₂. After 24 h, transfections are performed with Lipofectamine (Gibco-BRL, Gaithersburg, MD) according to the instructions of the manufacturer. Transfection mixes contain 0.00075 μ g of PPAR γ /GAL4 or PPAR α /GAL4 expression vector, 0.045 μ g of reporter vector
20 pUAS(5X)-tk-luc and 0.0002 μ g of pCMV-lacZ vector as an internal control of transfection efficiency. Compounds are characterized by incubation with transfected cells for 48h across a range of 8-12 concentrations from 0.1 nM to 50 μ M. Cell lysates are prepared from washed cells using Reporter Lysis Buffer (Promega) according to the manufacturer's directions. Luciferase activity in cell extracts is determined using
25 Luciferase Assay Buffer (Promega) in a ML3000 luminometer (Dynatech Laboratories). β -galactosidase activity is determined using β -D-galactopyranoside (Calbiochem-Novabiochem, LaJolla, CA) as described by Hollons and Yoshimura (Anal. Biochem, 182,411-418, 1989). Rosiglitazone can be used as a standard for human PPAR γ activity. EC₅₀ values for Rosiglitazone in the hPPAR γ /GAL4 assay
30 usually range from 20-40 nM. Fenofibrate can be used as a standard for hPPAR α activity. EC₅₀ values for Fenofibrate in the hPPAR α /GAL4 assay usually range from 5-20 μ M. Similarly, methods involving the co-transfection of full-length PPAR γ or PPAR γ along with a relevant reporter gene into one of several mammalian (or yeast) cell types can be employed as an alternative method to identify compounds with both
35 PPAR α and PPAR γ agonist activity.

Cell-Free Co-Activator Association Assay

- This assay measures the ability of compounds to promote the association of PPAR γ (or its isolated ligand binding domain) or PPAR α (or its isolated ligand binding domain) with a protein (or portion of a protein) that is (or is derived from) a co-activator molecule such as Creb Binding Protein (CBP) or Steroid Receptor Coactivator 1 (SRC-1) and can be used to identify compounds with both PPAR α and PPAR γ agonist activity. This assay is described in: Zhou G, Cummings R, Li Y, Mitra S, Wilkinson H, Elbrecht A, Hermes JD, Schaeffer JM, Smith RG, Moller DE. Nuclear receptors have distinct affinities for co-activators: characterization by fluorescence resonance energy transfer. *Mol Endocrinol* 1998 12:1594-1604, herein incorporated by reference in its entirety.

Human PPAR α and PPAR γ binding assays

- An alternative to measuring agonist activity of compounds in cell-based transactivation assays or cell-free co-activator association assays is to determine that compounds can function as ligands by binding to both PPAR γ and PPAR α . Compounds with half-maximal concentration potencies (IC₅₀'s or KI's) for displacement of radioligand binding to hPPAR γ vs. hPPAR α that differ by less than 30-fold and preferably less than 10-fold can be considered as dual ligands. For these assays, the methods described below can be employed (as also described in: Berger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Cullinan CA, Hayes NS, Li Y, Tanen M, Ventre J, Wu MS, Berger GD, Mosley R, Marquis R, Santini C, Sahoo SP, Tolman RL, Smith RG, Moller DE. Novel peroxisome proliferator-activated receptory (PPAR γ) and PPAR δ ligands produce distinct biological effects, 1999 *J Biol Chem* 274: 6718-6725.

- Human PPAR γ_2 and human PPAR α are expressed as a GST-fusion protein in *E. coli*. The full length human cDNA for PPAR γ_2 is subcloned into the pGEX-2T expression vector (Pharmacia). The full length human cDNA for PPAR α is subcloned into the pGEX-KT expression vector (Pharmacia). *E. coli* containing the respective plasmids were propagated, induced, and harvested by centrifugation. The resuspended pellet is broken in a French press and debris is removed by centrifugation at 12,000Xg. Recombinant human PPAR receptors are purified by affinity chromatography on glutathione sepharose. After application to the column, and one

wash, receptor is eluted with glutathione. Glycerol (10%) is added to stabilize the receptor and aliquots are stored at -80 °C.

For each assay, an aliquot of receptor is incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 µL/100 ml 8-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 µg/mL aprotinin, 2 µg/mL leupeptin, 2 µg/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 10 nM [³H] L-746,962, (21 Ci/mmol), ± test compound. Assays are incubated for ~16 hr at 4 °C in a final volume of 150 µL. Unbound ligand is removed by incubation with 100 µL dextran/gelatin-coated charcoal, on ice, for 10 min. After centrifugation at 3000 rpm for 10 min at 4 °C, 50 µL of the supernatant fraction was counted in a Topcount. In this assay the K_D for L-746,962 is ≈ 1 nM.

For a human PPARα binding assay, an aliquot of receptor is incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 µL/100 ml 8-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 µg/mL aprotinin, 2 µg/mL leupeptin, 2 µg/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 5.0 nM [³H]L-783483, ± test compound. Assays are incubated for ~16 hr at 4 °C in a final volume of 150 µL. Unbound ligand is removed by incubation with 100 µL dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4 °C, 50 µL of the supernatant fraction is counted in a Topcount.

Cell Proliferation Assay

This assay measures the ability of cells to convert MTS tetrazolium into formazan, using the AQueous cell proliferation assay kit (Promega, Madison, WI). This conversion is presumably accomplished by NADPH or NADH produced by dehydrogenase enzymes in metabolically active cells. The assay is described in Shu, et al., *Biochemical and Biophysical Research Communications*, vol. 267, pp. 345-349 (2000).

WHAT IS CLAIMED IS:

1. A method of treating or ameliorating hyperglycemia, treating or ameliorating one or more lipid disorders, or both in a patient having type 2 diabetes, comprising the step of:
Administering to the patient a therapeutically effective amount of a first drug which is a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinyl alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, (7) an ACAT inhibitor, and (8) a CTEP inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.
2. A method of treating or ameliorating hyperglycemia in a patient having type 2 diabetes as recited in Claim 1, comprising the step of:
Administering to the patient a therapeutically effective amount of a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinyl alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, (7) an ACAT inhibitor, and (8) a CTEP inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.
3. A method of treating or ameliorating one or more lipid disorders in a patient having type 2 diabetes as recited in Claim 1, comprising the step of:
Administering to the patient a therapeutically effective amount of a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinyl alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, (7) an ACAT inhibitor, and (8) a CETP inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

4. The method as recited in Claim 3, wherein the lipid disorder is selected from the group consisting of mixed dyslipidemia, diabetic dyslipidemia, hyperlipidemia, isolated hypercholesterolemia, elevated LDL-cholesterol and/or non-HDL-cholesterol, elevated hyperapoB lipoproteinemia, hypertriglyceridemia, elevated triglyceride-rich-lipoproteins, and low HDL cholesterol.

5. A method of concurrently treating or ameliorating hyperglycemia and one or more lipid disorders in a patient having type 2 diabetes as recited in Claim 1, comprising the step of :

10 Administering to the patient a therapeutically effective amount of a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, (7)
15 an ACAT inhibitor, and (8) a CTEP inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

6. A method of treating or ameliorating hyperglycemia, treating or ameliorating one or more lipid disorders, or both in a non-diabetic patient having insulin resistance or impaired glucose tolerance, comprising the step of:

20 Administering to the patient a therapeutically effective amount of a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, and
25 (7) an ACAT inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

7. A method of treating or ameliorating one or more lipid disorders in a non-diabetic patient having insulin resistance or impaired glucose tolerance as recited in Claim 6, comprising the step of:

30 Administering to the patient a therapeutically effective amount of a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic alcohol,
35

nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, and (7) an ACAT inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

5 8. The method as recited in Claim 7, wherein the lipid disorder is selected from the group consisting of mixed dyslipidemia, diabetic dyslipidemia, hyperlipidemia, isolated hypercholesterolemia, elevated LDL-cholesterol and/or non-HDL-cholesterol, elevated hyperapoB lipoproteinemia, hypertriglyceridemia, elevated triglyceride-rich-lipoproteins, and low HDL cholesterol.

10

 9. A method of ameliorating two or more coronary risk factors of metabolic syndrome in a patient diagnosed as having at least three defining risk factors of the ATP III definition of metabolic syndrome, wherein the coronary risk factors are abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, high blood pressure, and elevated fasting glucose, comprising the step of

15

 Administering to the patient a therapeutically effective amount of a PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic alcohol, 20 nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, and (7) an ACAT inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

 10. A method of ameliorating at least one coronary risk factor in a 25 patient diagnosed as having at least three defining risk factors of the ATP III definition of metabolic syndrome, wherein the coronary risk factors are abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, high blood pressure, and elevated fasting glucose as recited in Claim 9, comprising the step of:

 Administering to the patient a therapeutically effective amount of a 30 PPAR α / γ dual agonist and a therapeutically effective amount of a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, and

(7) an ACAT inhibitor, including pharmaceutically acceptable salts of one or more of the active ingredients.

11. A method as recited in any of Claims 1-10, wherein the
5 PPAR α/γ dual agonist is a balanced PPAR α/γ dual agonist.

12. A method as recited in Claim 11, wherein the PPAR α/γ dual
agonist is KRP-297.

10 13. A method as recited in any of Claims 1-10, wherein the second
drug is a cholesterol absorption inhibitor.

14. A method as recited in any of Claims 1-10, wherein the second
drug is a statin.
15

15. A method as recited in any of Claims 1-10, wherein the second
drug is an ACAT inhibitor.

16. A method as recited in any of Claims 1-10, wherein the second
20 drug is a fibrate.

17. The method as recited in Claim 11, wherein the PPAR α/γ dual
agonist is KRP-297 and the cholesterol absorption inhibitor is ezetimibe.

25 18. The method as recited in Claim 11, wherein the PPAR α/γ dual
agonist is KRP-297 and the second drug is a statin selected from the group consisting
of simvastatin, atorvastatin, lovastatin, pravastatin, rosuvastatin, and fluvastatin.

19. The method as recited in Claim 18, wherein the second drug is
30 simvastatin.

20. The method as recited in Claim 11, wherein the PPAR α/γ dual
agonist is KRP-297 and the second drug is selected from avasimibe, fenofibrate,
bezafibrate, clofibrate, and gemfibrozil.
35

21. A method of treating or ameliorating (1) hyperglycemia resulting from type 2 diabetes, and (2) one or more lipid disorders selected from dyslipidemia, hyperlipidemia, and hypercholesterolemia, as recited in Claim 1, said method comprising the administration of a combination of a therapeutically effective
5 amount of KRP-297 and a therapeutically effective amount of ezetimibe, or a pharmaceutically acceptable salt of one or both compounds, to a type 2 diabetic patient in need of treatment.

22. A pharmaceutical composition comprising
10 (a) a PPAR α / γ dual agonist;
(b) a drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotinic acid, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, and (7) an ACAT inhibitor, including pharmaceutically acceptable salts of one or more of
15 the active ingredients; and
(c) a pharmaceutically acceptable carrier.

23. A pharmaceutical composition as recited in Claim 22, said composition consisting essentially of KRP-297 or a pharmaceutically acceptable salt thereof, ezetimibe or a pharmaceutically acceptable salt thereof, and a
20 pharmaceutically acceptable carrier

24. A pharmaceutical composition as recited in Claim 22, said composition consisting essentially of KRP-297 or a pharmaceutically acceptable salt thereof, simvastatin or a pharmaceutically acceptable salt thereof, and a
25 pharmaceutically acceptable carrier.

25. A pharmaceutical composition as recited in Claim 22 consisting essentially of KRP-297 or a pharmaceutically acceptable salt thereof, ezetimibe or a
30 pharmaceutically acceptable salt thereof, simvastatin or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition comprising:
(1) a PPAR α / γ dual agonist;

- (2) a second drug selected from the group consisting of (1) a cholesterol absorption inhibitor, (2) an HMG-CoA reductase inhibitor, (3) a bile acid sequestrant, (4) nicotiny alcohol, nicotinic acid or a salt thereof, (5) a PPAR α agonist, (6) a phenolic anti-oxidant, and (7) an ACAT inhibitor, including pharmaceutically acceptable salts thereof; and
- 5 (3) a third drug selected from (a) insulin sensitizers, which are selected from (i) PPAR γ agonists; (ii) biguanides; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;
- 10 (b) insulin or insulin mimetics;
(c) sulfonylureas;
(d) α -glucosidase inhibitors;
(e) PPAR δ agonists;
(f) antiobesity compounds (anorectics);
- 15 (g) an ileal bile acid transporter inhibitor; and
(h) anti-inflammatory agents selected from aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 (COX-2) selective inhibitors.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/11896

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/426 A61K31/216 A61K31/22 A61K31/397 A61P3/10
A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, PASCAL, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 26729 A (BOUERES JULIA K ;DESAI RANJIT C (US); KOYAMA HIROO (US); MERCK & C) 4 April 2002 (2002-04-04)	1-12, 22, 26
Y	page 6, line 12 - line 24 page 14, line 23 -page 15, line 27 page 20, line 23 -page 22, line 20 claims 27-46	1-26
X	WO 02 08188 A (JONES ANTHONY BRIAN ;WOOD HAROLD BLAIR (US); MERCK & CO INC (US);) 31 January 2002 (2002-01-31)	1-12, 22, 26
Y	page 6, line 17 - line 33 page 24, line 26 -page 26, line 5 page 28, line 27 -page 30, line 6 claims 20-38	1-26
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

29 July 2003

Date of mailing of the international search report

07/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fayos, C

Intern	Application No
PCT/US	03/11896

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern # Application No
PCT/US 03/11896

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	SORBERA L A ET AL: "Netoglitzazone: Antidiabetic PPAR'alpha!/PPAR'gamma! agonist" DRUGS OF THE FUTURE 2002 SPAIN; vol. 27, no. 2, 2002, pages 132-139, XP009013693 ISSN: 0377-8282 published 22.04.02 the whole document	1-26
P,X	WO 02 064094 A (DROPINSKI JAMES F ;BERGER JOEL P (US); JONES A BRIAN (US); LIU KUN) 22 August 2002 (2002-08-22)	1-12,22, 26
Y	page 1, line 6 - line 10 page 21, line 21 -page 22, line 25 page 28, line 9 -page 30, line 7 page 32, line 29 -page 34, line 9 claims 24-43	1-26

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/US 03/11896

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0226729	A	04-04-2002	AU 9287401 A CA 2423141 A1 EP 1324995 A2 WO 0226729 A2 US 2002082292 A1	08-04-2002 04-04-2002 09-07-2003 04-04-2002 27-06-2002
WO 0208188	A	31-01-2002	AU 7705601 A CA 2415742 A1 EP 1305285 A1 WO 0208188 A1 US 2002042441 A1	05-02-2002 31-01-2002 02-05-2003 31-01-2002 11-04-2002
WO 0160807	A	23-08-2001	AU 3821401 A CA 2400021 A1 EP 1259494 A1 WO 0160807 A1 US 2002173663 A1	27-08-2001 23-08-2001 27-11-2002 23-08-2001 21-11-2002
US 6030990	A	29-02-2000	JP 3144624 B2 JP 9048771 A AT 212341 T AU 698896 B2 AU 5844696 A CA 2220698 A1 CA 2417403 A1 CA 2417408 A1 CN 1336366 A CN 1186489 A , B DE 69618792 D1 DE 69618792 T2 DK 846693 T3 EP 0846693 A1 ES 2170858 T3 HU 9802565 A2 WO 9638428 A1 JP 2001139565 A PT 846693 T TW 400328 B US 6001862 A US 6147101 A	12-03-2001 18-02-1997 15-02-2002 12-11-1998 18-12-1996 05-12-1996 05-12-1996 05-12-1996 20-02-2002 01-07-1998 14-03-2002 10-10-2002 06-05-2002 10-06-1998 16-08-2002 28-04-1999 05-12-1996 22-05-2001 31-05-2002 01-08-2000 14-12-1999 14-11-2000
US 6166049	A	26-12-2000	AU 1439797 A BG 102668 A BR 9706968 A EP 0879053 A1 JP 2000503643 T NO 983147 A PL 327731 A1 SK 92598 A3 CA 2242632 A1 CN 1212622 A CZ 9802163 A3 WO 9725042 A1 HU 9900560 A2 NZ 502966 A TR 9801315 T2 ZA 9700171 A	01-08-1997 30-04-1999 06-04-1999 25-11-1998 28-03-2000 08-09-1998 21-12-1998 11-01-1999 17-07-1997 31-03-1999 17-02-1999 17-07-1997 28-07-1999 30-11-2001 21-10-1998 24-07-1998

INTERNATIONAL SEARCH REPORT

Intern	Application No
PCT/US 03/11896	

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0134148	A	17-05-2001	AU 1304601 A CA 2390557 A1 EP 1243266 A1 WO 0134148 A1	06-06-2001 17-05-2001 25-09-2002 17-05-2001
WO 0114351	A	01-03-2001	AU 6594700 A CA 2382573 A1 CN 1382128 T EP 1207157 A1 HU 0202701 A2 WO 0114351 A1	19-03-2001 01-03-2001 27-11-2002 22-05-2002 28-12-2002 01-03-2001
WO 02064094	A	22-08-2002	WO 02064094 A2	22-08-2002

